REMARKS

Claims 1-19 and 21-31 are pending in the application. Claims 15, 26 and 29-31 have been withdrawn as being directed to non-elected subject matter. Claims 1-4, 6-14, 16-19, 21-25, 27 and 28 were rejected. Claims 5 and 6 were objected to. No claims were allowed. In this response, claims 1-4, 6-12, 21-23 and 27-31 are amended, and support for these amendments can be found throughout the application as-filed (e.g., see paragraph [0008], Example 1 and Example 6). No claims have been added or canceled. Thus, claims 1-14, 16-19, 21-25, 27 and 28 are currently under consideration. The amendments made herein are made solely for responding to this Office Action and are not to be construed as acquiescing to the Examiner's position nor surrender of any subject matter. Applicants reserve the right to pursue the amended or canceled subject matter in one or more divisional or continuation applications. No new matter has been added by virtue of these amendments and entry is respectfully requested.

Claim Objections

Applicants thank the Examiner for the telephonic interview on December 16, 2011, to clarify the claim objections and for the Interview Summary regarding same. According to the Examiner and the Interview Summary, claim 5, rather than claim 15 (as erroneously indicated on page 3 of the Office Action) was objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims. Claim 5 depends from claim 3 which Applicants assert is allowable as amended herein.

In view of the foregoing, Applicants respectfully request withdrawal of the Examiner's objection.

Claim 6 was objected to because the word "sequence" appears to be missing in line 3 after the word "translocating." Claim 6 is amended herein to recite "translocating sequence."

In view of the foregoing, Applicants respectfully request withdrawal of the Examiner's objection.

Claim Rejections Under 35 U.S.C. § 112

Claims 12-14, 16-19, and 21-25 were rejected under 35 U.S.C. § 112, first paragraph. According to the Office Action, the specification does not reasonably provide enablement for a method of treating an inflammatory disease in a subject wherein the subject is at risk for presenting with an inflammatory disease. Applicants respectfully disagree with this rejection. A method of treating an inflammatory disease in a subject wherein the subject is at risk for presenting with an inflammatory disease is enabled throughout the specification including paragraphs 106-107, 133-136, 137, 144, 149-153, 154, 156, 177, and 178. The disclosed method of treating a subject suffering from an inflammatory disease is the same for treating a subject at risk for presenting with an inflammatory disease. Example 5 is a working example of treating an inflammatory disease in a subject wherein the subject is at risk for presenting with an inflammatory disease. In Example 5, administering the CP-SOCS3 protein produced a protective effect against exposure to SEB-like superantigens and D-galactosamine. SEB-like superantigens are known to produce an acute systemic inflammatory response, including liver injury. In addition, paragraph 107 states "[f]ollowing administration of a disclosed composition, such as SOCS sequences or a cell-penetrating SOCS sequences, for treating, inhibiting, or preventing inflammation, for example , the efficacy of a therapeutic antibody can be assessed in various ways well known to the skilled practitioner." Although claims 12 and 23 do not recite "wherein the subject is at risk for presenting with an inflammatory disease," Applicants interpret the paragraph spanning pages 4 and 5 of the Office Action to mean that the Examiner considers claims 12 and 23 to encompass a prophylactic treatment of an inflammatory disease in a subject who is at risk for inflammation.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claim Rejections Under 35 U.S.C. § 103

Claims 1-4, 6-11, 27, and 28 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Hilton *et al.* (US Patent 6,323,317) in view of Lin *et al.* (WO 99/49879) for the reasons set forth in the previous office actions. Applicants again respectfully disagree with this rejection. However, solely to expedite prosecution of the present application, claims 1-4, 6-11, 27, and 28 are amended herein to recite "a soluble polypeptide" or "a soluble isolated polypeptide."

As the Examiner has acknowledged, Hilton *et al.* do not teach a polypeptide comprising a SOCS sequence and a membrane translocating sequence. In addition, the Examiner has acknowledged that Hilton *et al.* also do not teach a nucleic acid encoding a polypeptide comprising a SOCS sequence and a membrane translocating sequence. Neither of the references provide any reasoning as to why these two particular proteins should be brought together in the manner taught by Applicants. Neither of these references, nor the combination thereof, provide any guidance or teachings to engineer the actual soluble proteins disclosed in the instant invention. The Hilton *et al.* and Lin *et al.* references do not teach or suggest a combination of the SOCS protein and a membrane translocating sequence that is soluble and isolated. In Examples 1 and 6 of the present application, production of soluble SOCS polypeptides by Applicants is described. As discussed in the Response filed June 3, 2010, combining SOCS1 or SOCS3 with an MTS could have resulted in a polypeptide that is insoluble, or in the failure to express a polypeptide at all. Applicants wish to emphasize the challenge of obtaining a soluble recombinant SOCS polypeptide as recited in the claims as amended herein. The generation of the claimed polypeptides was thus unexpected and unpredictable. Lin *et al.* does not demonstrate successful import of a SOCS protein. Filed herewith is Applicants' paper (DiGiandomenico *et al.*) Intracellular Delivery of a Cell-Penetrating SOCS1 that Targets IFN-γ Signaling, Science Signaling, 2(80), ra37 (2009)). At paragraph 1 on page 7, this paper states "[i]t is noteworthy that SOCS1 proteins taken out of their intracellular milieu require protein stabilizers, such as L-arginine, a powerful suppressor of protein aggregation, to maintain protein solubility." DiGiandomenico *et al.*, at p. 7. Therefore, Lin *et al.* does not teach how to obtain an isolated soluble polypeptide comprising a SOCS sequence and a membrane translocating sequence. The expression protocol disclosed in Lin *et al.* may teach an isolated

soluble polypeptide for the polypeptides disclosed therein, but it does not teach that the protocol described therein would yield an isolated soluble polypeptide comprising a SOCS sequence and a membrane translocating sequence.

Applicants respectfully submit that this evidence of unexpected properties argues strongly against obviousness (*See* MPEP § 2145) and that such an unexpected result is sufficient to overcome obviousness in accordance with MPEP § 2145. In accordance with the Manual of Patent Examining Procedure (MPEP):

> Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties . . . Evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a prima facie case of obviousness.

MPEP § 2145.

The present rejection appears to be based on the grounds that some teaching, suggestion or motivation exists in the prior art that would have led one of ordinary skill to modify the prior art references or to combine prior art teachings to arrive at the claimed invention, and that the skilled artisan would have a reasonable expectation of success. Applicants respectfully submit: a) there is no explicit or implicit teaching or motivation in Hilton et al. nor Lin et al., even when combined, to pick and choose the present claim limitations from each of these references and combine them; and b) the claimed combination yielded more than predictable results. Applicants are aware of *KSR International Co. v. Teleflex, Inc.*, as well as the USPTO's Examination Guidelines Update: Developments in the Obviousness Inquiry After *KSR* v. *Teleflex* issued on September 1, 2010, in the Federal Register (hereinafter "the Guidelines"). Example 4.2 of the Guidelines refers to *Crocs, Inc.*v. *U.S. International Trade Commission*, 598 F.3d 1294 (Fed. Cir. 2010). According to Example 4.2 of the Guidelines, "[a] claimed combination of prior art elements may be nonobvious where the prior art teaches away from the claimed combination and the combination yields more

than predictable results." In *Crocs, Inc.*, The Federal Circuit stated that even if all elements of the claimed invention had been taught by the prior art, the claims would not have been obvious because the combination yielded more than predictable results. Also according to the Guidelines in its discussion of *Crocs, Inc.*, "[i]f results would not have been predictable, Office personnel should not enter an obviousness rejection using the combination of prior art elements rationale, and should withdraw such a rejection if it has been made." As described herein, the claimed compositions and methods yielded unexpected results, and Applicants assert that these unexpected results evidence that the claimed subject matter would have been unobvious in view of the cited combination of references and the knowledge of one skilled in the art. Applicants submit that one of skill in the art, based on his or her own knowledge and the cited combination of references, would *not* be motivated to combine a SOCS polypeptide with an MTA resulting in a soluble polypeptide that provides for controlled delivery of SOCS for the replacement of depleted stores of intracellular physiologic protein.

Based on the foregoing, the cited references in combination do not render the present invention obvious within the meaning of 35 U.S.C. 103. Applicants submit that the claimed invention yielded unexpected results, and that one of skill in the art at the time the invention was made would not have arrived at the claimed invention even in view of the cited references.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 12-14, and 23-25 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Shouda *et al.* (*J. Clin. Invest* 108(12): 1781-1788, 2001) in view of Hilton *et al.* (US Patent 6,323,317) and Lin *et al.* (WO 99/49879) for the reasons set forth in the previous office actions. Applicants again respectfully disagree with this rejection. However, solely to expedite prosecution of the present application, claims 12 (from which claims 13 and 14 depend) and 23 (from which claims 24 and 25 depend) are amended herein to recite "a soluble isolated polypeptide."

For the reasons set forth above, the combination of Hilton *et al.* and Lin *et al.* fails to render claims 12-14, and 23-25 obvious. The addition of Shouda et al. fails to remedy the deficiencies of

Hilton *et al.* and Lin *et al.* As asserted previously, the Examiner has acknowledged that Shouda *et al.* do not teach a recombinant protein comprising a SOCS sequence and a membrane translocating sequence. As discussed above, it would not be obvious to one of ordinary skill in the art to combine SOCS and MTS including the Shouda *et al* study. In addition, since SOCS has a very short half-life, and assuming *arguendo*, that one of ordinary skill in the art did combine Hilton et al. and Lin et al., one of skill in the art would rather incorporate the SOCS in an expression vector so as to prevent the degradation of SOCS until the expression vector containing the SOCS nucleic acid sequence was in the cell. With Shouda *et al.*, further describing the use of vectors to express proteins, one of skill in the art would be *taught away* from using a protein with a very short half-life in the treatment of inflammatory diseases. Rather, one of skill in the art would be directed to a vector expressing such a SOCS protein. Thus, neither Hilton *et al.* in view of Lin *et al.* provide the necessary motivation to combine the SOCS and MTS as taught by Applicants. This is in stark contrast to Applicants invention which is directed *inter alia*, to the importation of the therapeutic **soluble** SOCS proteins into cells and can be systemically disseminated throughout various cells, tissues, organs and fluids rendering a superior therapy.

Applicants further assert it would not be obvious to modify the gene transfer method of treating rheumatoid arthritis of Shouda *et al.* with a fusion polypeptide of the SOCS sequence of Hilton *et al.* and the membrane translocation sequence of Lin *et al.* because Shouda *et al.* does not teach the injection protocol for a fusion polypeptide, including the amount to inject, for its method. Shouda *et al.* discloses the amount of recombinant virus comprising a Myc-tagged CIS3 gene to inject, not the injection amount of an isolated soluble polypeptide comprising SOCS1 or SOCS3 and a membrane translocating sequence. One of skill in the art would *not* have combined these references because Shouda *et al.* utilizes an adenovirus vector comprising SOCS3 DNA as opposed to a polypeptide comprising a SOCS sequence and a membrane translocating sequence.

Applicants again wish to emphasize that the generation of the claimed polypeptides was unexpected and unpredictable. The engineered proteins taught by Applicants provide for controlled delivery of SOCS for the replacement of depleted stores of intracellular physiologic protein, a feasible alternative to gene transfer of SOCS3. Also unexpectedly, Applicants have been able to

provide for the "**controlled delivery**" of the SOCS protein resulting in one of skill in the art to be able to correctly dose the amount of SOCS needed for therapy. One of skill in the art based on the combination of cited references would not conceive of importing protein with a very short half-life, especially a soluble protein whose level of expression in the target cell could be controlled. Without the guidance and teachings of the instant invention, these two references fail to rise to the level of obviousness, even in view of *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

Based on the foregoing, the cited references in combination do not render the present invention obvious within the meaning of 35 U.S.C. 103. Applicants submit that the claimed invention yielded unexpected results, and that one of skill in the art at the time the invention was made would not have arrived at the claimed invention even in view of the cited references.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

CONCLUSION

Applicants invite the Examiner to call the undersigned if it is believed that a telephonic interview will expedite the prosecution of the application to an allowance.

The Commissioner for Patents and Trademarks is hereby authorized to charge any deficiency or credit any overpayment in any fees paid on the filing, or during prosecution of this application to Deposit Account No. 14-1437.

Dated: January 11, 2012

/Amy A. Dobbelaere/

Amy A. Dobbelaere, Ph.D.
Registration No. 52,088
NOVAK DRUCE+ QUIGG, LLP
CityPlace Tower
525 Okeechobee Blvd., 15th Floor
West Palm Beach, FL 33401
Phone: 561-847-7809
Fax: 561-847-7801